Dexmedetomidine infusion for analgesia up to 48 hours after lung surgery performed by lateral thoracotomy

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Patients undergoing a lateral thoracotomy for pulmonary resection have moderate to severe pain postoperatively that is often treated with opioids. Opioid side effects such as respiratory depression can be devastating in patients with already compromised respiratory function. This prospective double-blinded clinical trial examined the analgesic effects and safety of a dexmedetomidine infusion for postthoracotomy patients when administered on a telemetry nursing floor, 24 to 48 hours after surgery, to determine if the drug's known early opioid-sparing properties were maintained. Thirty-eight thoracotomy patients were administered dexmedetomidine intraoperatively and overnight postoperatively and then randomized to receive placebo or dexmedetomidine titrated from 0.1 to 0.5 $\mu g \cdot kg \cdot h^{-1}$ the day following surgery for up to 24 hours on a telemetry floor. Opioids via a patient-controlled analgesia pump were available for both groups, and vital signs including transcutaneous carbon dioxide, pulse oximetry, respiratory rate, and pain and sedation scores were monitored. The dexmedetomidine group used 41% less opioids but achieved pain scores equal to those of the placebo group. The mean heart rate and systolic blood pressure were lower in the dexmedetomidine group but sedation scores were better. The mean respiratory rate and oxygen saturation were similar in the two groups. Mild hypercarbia occurred in both groups, but periods of significant respiratory depression were noted only in the placebo group. Significant hypotension was noted in one patient in the dexmedetomidine group in conjunction with concomitant administration of a beta-blocker agent. The placebo group reported a higher number of opioid-related adverse events. In conclusion, the known opioid-sparing properties of dexmedetomidine in the immediate postoperative period are maintained over 48 hours.

The provision of excellent and safe postoperative pain management for patients who have undergone a major thoracotomy for lung or partial lung resection is challenging. Inadequate pain control may result in splinting of the chest, poor chest excursion, atelectasis, and respiratory failure. Pain management based on an opioid-based protocol runs the risk of adverse drug events related to narcotics. Several recent reports have demonstrated that respiratory depression and deep levels of sedation can occur when morphine patient-controlled analgesia (PCA) is prescribed (1–7). The patient with compromised pulmonary function may be at an increased risk for an adverse event.

Dexmedetomidine, an alpha 2-adrenoceptor agonist, has been used to provide sedation in critical care patients and has been demonstrated to reduce opioid requirements, cause minimal respiratory depression, and improve outcomes (8–22). We hypothesized that the addition of a dexmedetomidine infusion to the postoperative pain management protocol would reduce the amount of morphine delivered by a PCA pump, reduce the opioid-induced adverse drug effects, and provide adequate analgesia for postthoracotomy patients. We also hypothesized that once the patient had been receiving dexmedetomidine for 24 hours, the infusion could be administered safely on a monitored telemetry unit as opposed to an intensive care unit (ICU) to maintain a good level of responsiveness and comfort, a Ramsay Sedation Score (RSS) of 2 to 4 (23), and hemodynamic stability. A prospective, double-blinded, controlled clinical pilot trial was designed to test these hypotheses.

METHODS

Institutional review board approval was obtained at Baylor University Medical Center at Dallas to enroll patients undergoing major open thoracotomy surgery between November 2006 and October 2007. All subjects were between 18 and 85 years of age and had an American Society of Anesthesiologists physical status of 3 or under. Subjects were excluded from enrollment if they had serious central nervous system pathology, a left ventricular ejection fraction of <30%, conduction abnormalities with the exception of first-degree atrioventricular block and rate-controlled atrial fibrillation, acute or chronic hepatitis, a requirement for renal supplementation, a known uncontrolled seizure disorder, a known or suspected physical or psychological dependence on an abused drug other than alcohol, or a psychiatric illness that would confound a normal response to sedative treatment or if they were pregnant or

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lactating. Prior to enrollment, subjects were screened for study eligibility. Informed consent was obtained prior to the initiation of any study procedures.

The medical history was reviewed and subjects underwent routine preoperative assessment and examination. The patients then underwent the standard anesthetic management for thoracic surgery at this institution. General anesthesia was induced with propofol, fentanyl, and sevoflurane and relaxation provided with vecuronium. Anesthesia continued utilizing one-lung ventilation with intraoperative fentanyl, sevoflurane, and an intraoperative infusion of dexmedetomidine at 0.2 to 0.5 $\mu g \cdot kg \cdot h^{-1}$ with no initial bolus. At the end of surgery, an injection of 5 cc ropivacaine 0.5% plain paravertebral block at levels T4, 5, 6, and 7 was provided. Patients emerged from the operating room extubated and awake with continuous local anesthetic wound infiltration delivered by an elastomeric infusion pump and stayed overnight in the ICU or postanesthesia care unit (PACU). Patients continued to receive dexmedetomidine intravenously titrated from 0.2 to 0.5 $\mu g \cdot kg \cdot h^{-1}$ during their ICU or PACU stay to provide adequate analgesia and comfort. Supplementary opioids were administered by a PCA pump.

Approximately 18 to 24 hours after surgery, patients were discharged from the ICU or PACU to the telemetry unit. Prior to discharge they were randomized to receive either normal saline or dexmedetomidine continuously infusing at a rate titrated between 0.1 and 0.5 $\mu g \cdot kg \cdot h^{-1}$ for up to 24 hours. A morphine PCA pump was available for both groups of patients. The intravenous dexmedetomidine infusion was stopped and the study drug was started in the ICU or PACU 30 minutes prior to transfer to the telemetry unit. Study infusion was titrated by 0.1 $\mu g \cdot kg \cdot h^{-1}$ increments in 30-minute intervals to maintain a pain score <5 on a 0 to 10 numeric pain scale, an RSS from 2 to 4, a systolic blood pressure >89 and <181 mm Hg, and a heart rate >49 and <111 beats per minute. The decision tree for titration is shown in *Figure 1*.

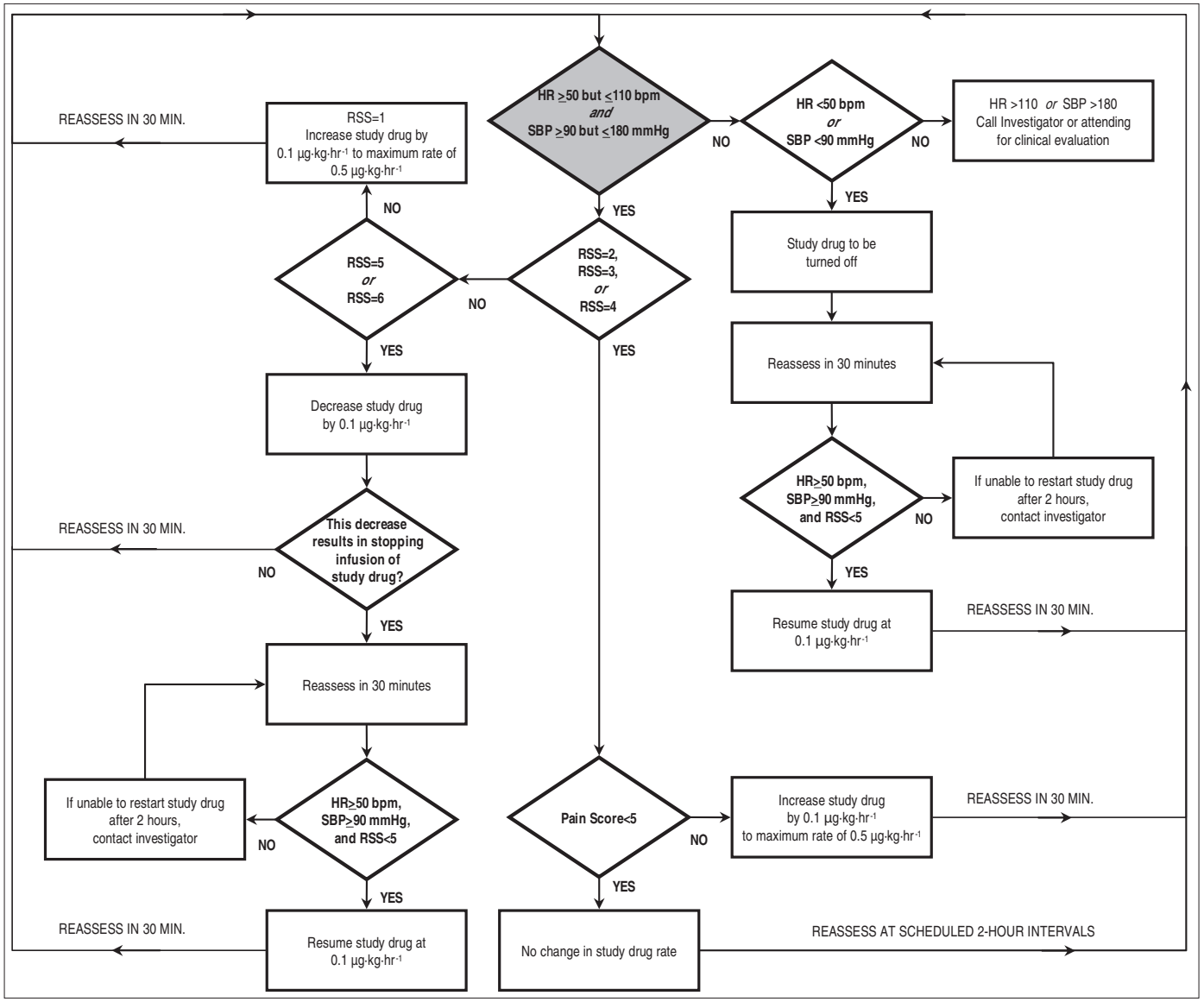

Figure 1. Titration decision tree.

Continuous electrocardiogram, pulse oximetry (SpO_2), and transcutaneous carbon dioxide ($tcpCO_2$) monitoring (TOSCA®, Radiometer, Copenhagen, Denmark) was in place while the patients were on the study drug. Blood pressure, heart rate, respiratory rate, SpO2, $tcpCO_2$, pain score, and RSS were assessed and recorded every 2 hours and immediately preceding and 30 minutes following study drug titration. If the study drug remained off for >4 hours, the patient was withdrawn from the study. Concomitant medications (including any concomitant vasoactive medication required), total opioids administered, and adverse events were recorded. The study drug was discontinued at hour 24 of infusion, which was approximately 42 to 48 hours postsurgery or when the prepared study drug expired, whichever was sooner.

This was a double-blind, placebo-controlled randomized superiority pilot study. The primary outcome of interest was the amount of self-administered opioid medication during 24 hours after PACU or ICU discharge and 24 to 48 hours after surgery. The active drug study group was treated with low-dose dexmedetomidine and the placebo group with saline. Secondary outcomes were average pain scores, average sedation level as measured by RSS, instances of respiratory depression and hemodynamic instability, and the adverse effects of dexmedetomidine in this patient group.

To calculate an appropriate sample size and baseline opioid use, a preparatory chart review study was conducted. The medical records of 10 patients who would be typical of those presenting to this study were reviewed for their opioid use in the first 24 hours after discharge from the ICU or PACU. Fentanyl, hydromorphone, and other opioids were converted to intravenous morphine sulfate equivalents (mg) *(Table 1)*. The data suggested that in a group of 10 thoracotomy patients, the amount of self-administered opioid in the first 24 hours post-PACU or ICU would range from 68 to 122.5 mg with a mean of 85 mg and a standard deviation of 20 mg. Of interest was to reduce the opioid use by half, i.e., to a mean value of 42.5 mg. Assuming that low-dose dexmedetomidine causes the average total opioid use during the first 24 hours post-PACU or ICU to be reduced to 42.5 mg, then 10 patients in each of the two treatment groups would be sufficient to demonstrate that difference as statistically significant at the type I and type II error rates of 0.05 and 0.10, respectively. Assuming that not more than 50% of enrolled patients would discontinue the drug prematurely, then a sufficient sample size for each group would need to include an additional 10 patients for a total enrollment of 40 subjects.

Table 1. Conversion of opioids to intravenous morphine sulfate equivalents

Opioid	Intravenous morphine sulfate equivalency
Hydrocodone 15 mg (oral)	9 mg
Hydromorphone 1.5 mg (intravenous)	10 mg
Fentanyl 75 mcg/hr (transdermal)	3 mg/hr
Meperidine 75 mg (intravenous)	10 mg
Fentanyl 100 mcg (intravenous)	10 mg

An interim unblinded analysis of the morphine sulfate use by study group was conducted after enrollment of 14 patients, 11 of which received study drug, to see if the results proved to be statistically significant, thus exposing a fewer number of subjects. This interim analysis determined that the premature discontinuation rate was higher than expected and the amount of variation in opioid use was larger than found in the preparatory chart review study. Taking into account the new estimate of variation and the unblinding of the 11 subjects randomized, a sufficient sample size for each group was estimated to be 19 patients.

A random permuted blocks design with a block size of eight was used to randomly allocate consented patients to the placebo or dexmedetomidine groups. An independent biostatistician provided the randomization scheme to the pharmacist to maintain the study as double blind.

A Student *t* test was used to evaluate the difference between the placebo and dexmedetomidine groups for the continuous variables such as the primary outcome of the amount of self-administered opioid medication during 24 hours post PACU or ICU and the secondary outcomes of infusion time, pain score, and vital signs. Chi-square analysis and Fisher exact test were utilized to evaluate the categorical variables such as gender and race. A P value of < 0.05 was considered significant.

RESULTS

A total of 51 patients signed the IRB-approved informed consent form, 32 women and 19 men with a mean age of 58 ± 13 years (± standard deviation). Thirteen of 51 were withdrawn from the study prior to randomization and start of the study drug: five were withdrawn because they did not have an overnight stay in the ICU or PACU, three withdrew consent, three had a serious adverse event and withdrawal was in their best interest, one was unable to be intubated and had surgery rescheduled, and one did not remain on dexmedetomidine overnight while in the ICU *(Figure 2)*. Study drug was started in 38 subjects, with 19 subjects randomized into each study group. The demographic characteristics were similar between the two study groups when comparing age, gender, weight, and race *(Table 2a)*.

The amount of time each group received study drug was equivalent, with the infusion amount and rate of early withdrawal similar between the two groups *(Table 2b)*. Four subjects were withdrawn early, with the study drug permanently stopped during the course of the infusion, due to withdrawn consent (n = 1), hypotension (n = 1), pneumonia (n = 1), and volume depletion (n = 1). The one subject withdrew consent after 245 minutes of study drug infusion because of the intensity of the required monitoring. The hypotensive subject, randomized to the dexmedetomidine group, received a concurrent beta-blocker and experienced sustained mild hypotension. The protocol was subsequently changed to exclude administering routine beta-blockers while on study drug. After

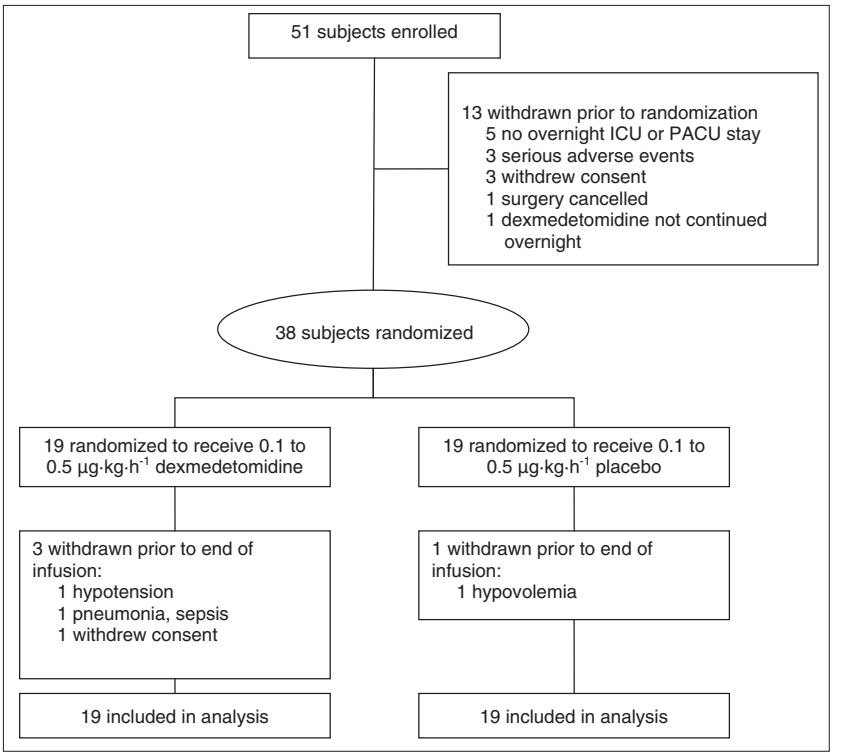

Figure 2. Participant flow.

750 minutes of study drug, the third patient, randomized to the dexmedetomidine group, was diagnosed with pneumonia and experienced tachycardia and hypotension. This patient was treated accordingly but was withdrawn from the study due to the sepsis syndrome that had developed. The fourth patient, randomized to the placebo group, was withdrawn from the study after the study drug had been off for 4 hours per protocol. This patient had the study drug stopped due to hypovolemia and hypotension. The blood pressure normalized with volume replacement that was initiated shortly after the 4-hour window.

The two groups were similar in the types of PCA pumps and supplemental opioids used *(Table 2c).* The results showed that the placebo group used 41% more total opioid in intravenous morphine equivalency than the dexmedetomidine group (P = 0.03) for the period of time on the study drug *(Table 2b).* When the opioid use was weighted for total time on study drug, the placebo group also used 35% more opioids than the dexmedetomidine group (P = 0.04). *Figure 3* shows the variability of opioid use presented in morphine equivalency by study group.

The mean systolic blood pressure and heart rate by patient were significantly lower in the dexmedetomidine group than in the placebo group (P = 0.008 and P = 0.01, respectively). The mean RSS between the groups was significant, as the placebo group had no scores above an RSS of 2 while the dexmedetomidine group had an RSS that ranged from 2 to 4, indicating a comfortable relaxed patient. The two groups were statistically similar when looking at the mean diastolic blood pressure, respiratory rate, pulse oximetry, $tcpCO_2$, and pain levels by patient *(Table 2d).*

No patients in either group had observed episodes of decreased respiratory rate. When looking at all recorded respiratory rates, the dexmedetomidine group had a larger percentage (49% vs 40%) of respiratory rates within the normal range of 10 to 18 breaths per minute *(Figure 4).* Placebo subjects had respiratory rates higher than the normal range more frequently than dexmedetomidine subjects (60% vs 51%), although this difference was not statistically significant (P = 0.08).

Comparing all subjects, the $tcpCO_2$ was in the normal range of 38 to 42 mm Hg for 24% of the time while receiving study drug. The $tcpCO_2$ was >42 mm Hg for 56% of the time for all subjects, and the mean $tcpCO_2$ was similar across the two groups when looking at all times combined (P = 0.58). During hours 6 to 16, the mean $tcpCO_2$ of the two groups was statistically different (42 ± 8 mm Hg vs 45 ± 9 mm Hg, P = 0.02) with a higher mean $tcpCO_2$ for the placebo group *(Figure 5).* During this same timeframe, the mean pain scores for the dexmedetomidine and placebo groups were similar (3 ± 2.3 vs 3 ± 2.2, P = 0.59), but the mean RSS was significantly different (2 ± 0.3 vs 2 ± 0, P = 0.006).

A total of 43 adverse events were reported for all 51 patients *(Table 3).* Three of the adverse events—which included cardiac arrest, multiple organ dysfunction syndrome, and Stokes-Adams attacks—necessitated subject withdrawal prior to randomization. The two episodes of bradycardia, defined as a heart rate <50 beats per minute, occurred in the same subject randomized to the placebo group and necessitated a short study drug interruption per protocol. The first episode was treated with 0.2 mg of glycopyrrolate intravenously and the second episode resolved without treatment.

In five separate instances, the study drug infusion was interrupted and then started again a short time later due to a systolic blood pressure of <90 mm Hg, one time in the placebo group and four times in the dexmedetomidine group. Study

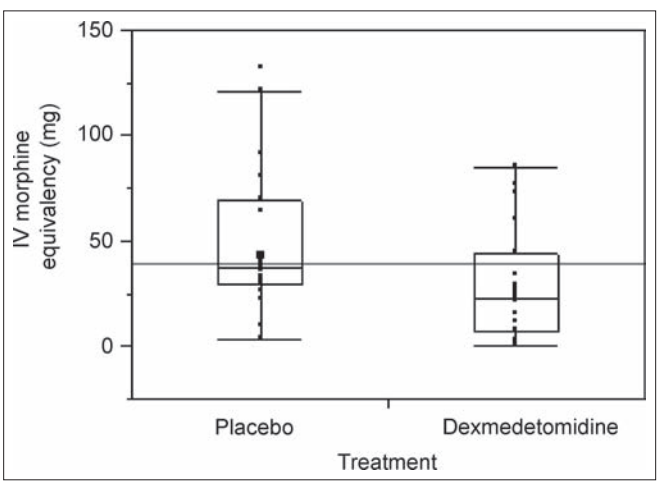

Figure 3. Total opioid use presented in intravenous morphine equivalency of subjects randomized to placebo compared to intravenous dexmedetomidine.

Table 2. Results for subjects randomized to placebo compared to intravenous dexmedetomidine

Variable	Placebo group (n = 19)	Dexmedetomidine group (n = 19)	*P* value
a. Demographic characteristics			
Age (years)	56 ± 13	61 ± 11	0.24
Male	7 (37%)	8 (42%)	1.0
Female	12 (63%)	11 (58%)	
Weight (kg)	79.4 ± 20.4	79.2 ± 14.8	0.97
Body mass index	25.8 ± 5.4	25.3 ± 4.8	
African American	0	1 (5%)	0.35
Asian	0	1 (5%)	
Caucasian	19 (100%)	17 (89%)	
b. Drug administration			
Total infusion time (minutes)	1281 ± 288	1214 ± 347	0.52
Total study drug administered (mcg)	496† ± 239	497 ± 268	0.50
Total study drug administered (mcg) adjusted to 24 hours	541 ± 257	576 ± 282	0.35
Early withdrawal			0.60
Consent withdrawn	—	1 (5%)	
Hypotension	—	1 (5%)	
Pneumonia	—	1 (5%)	
Volume depletion	1 (5%)	—	
IV morphine equivalency administered (mg)	49 ± 35	29 ± 26	0.03*
IV morphine equivalency administered (mg) adjusted for total time on study drug	54 ± 37	35 ± 28	0.04*
c. Type of opioid use			
PCA	Morphine sulfate: 18	Morphine sulfate: 17	
	Hydromorphone: 1	Hydromorphone: 2	
Supplemental opioids	Hydrocodone: 3	Hydrocodone: 4	
	Meperidine (IV): 1	Hydromorphone: 1	
	Hydrocodone/fentanyl (IV): 1	Fentanyl (transdermal): 1	
d. Vital signs			
Systolic blood pressure (mm Hg)	125 ± 11.4	114 ± 11.1	0.008*
Diastolic blood pressure (mm Hg)	65 ± 7.4	64 ± 5.3	0.41
Heart rate (beats per minute)	90 ± 12.3	80 ± 12.3	0.01*
Respiratory rate (breaths per minute)	20 ± 2.8	19 ± 2.3	0.41
Pulse oximetry (%)	98 ± 1.6	97 ± 1.7	0.13
Transcutaneous carbon dioxide (mm Hg)	44 ± 5.3	43 ± 6.7	0.58
Pain score	3 ± 1.7	3 ± 2.3	0.52
Ramsay Sedation Scale	2 ± 0.1	2 ± 0.1	0.01*

*$P < 0.05$.
†Calculated based on infusion rates assuming concentration of dexmedetomidine group.
Data are presented as mean ± standard deviation or n (%).

drug was resumed only with a systolic blood pressure of >89 mm Hg and after a minimum of 30 minutes and no longer than 4 hours had passed. Three of the five subjects, one in the placebo group and two in the dexmedetomidine group, did not require any interventions, and the study drug was resumed with no further complications. One dexmedetomidine subject experienced mild hypotension and had the study drug interrupted and restarted 30 minutes later with no interventions. Five and a half hours later, this same subject experienced hypotension and the study drug was interrupted. The study drug remained off and the subject was withdrawn from the study due to pneumonia and the sepsis syndrome that had developed. This same subject also was the one dexmedetomidine subject to experience tachycardia. A second dexmedetomidine subject had the study drug interrupted due to hypotension, which required treatment of a 250 mL normal saline bolus. The study drug was resumed 95 minutes later. This subject was withdrawn from the study 70 minutes after the second start of the study drug when it was discovered that a concurrent beta-blocker had been administered and the subject experienced a second episode of hypotension.

Adverse events associated with opioid administration such as constipation, nausea, and pruritus were reported in greater numbers in the placebo group (placebo = 12 vs dexmedetomidine = 4). The odds ratio of developing one of these side effects in the dexmedetomidine group was 0.3 compared with the placebo group, with a 95% confidence interval of (0.07, 1.23).

DISCUSSION

The standard procedure for managing postoperative pain for thoracotomy patients in this institution is to provide a paravertebral regional block with an injection of 5 cc ropivacaine 0.5% at levels T4 to T7 at the end of surgery. This is supplemented in the first 24 hours by an infusion of dexmedetomidine, and PCA morphine is also available. While opioids produce the added analgesia, they also cause respiratory depression that is particularly concerning in patients who

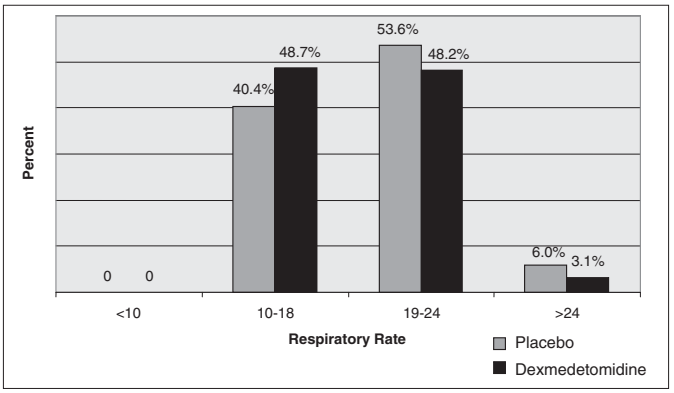

Figure 4. Respiratory rates between subjects randomized to placebo compared to intravenous dexmedetomidine.

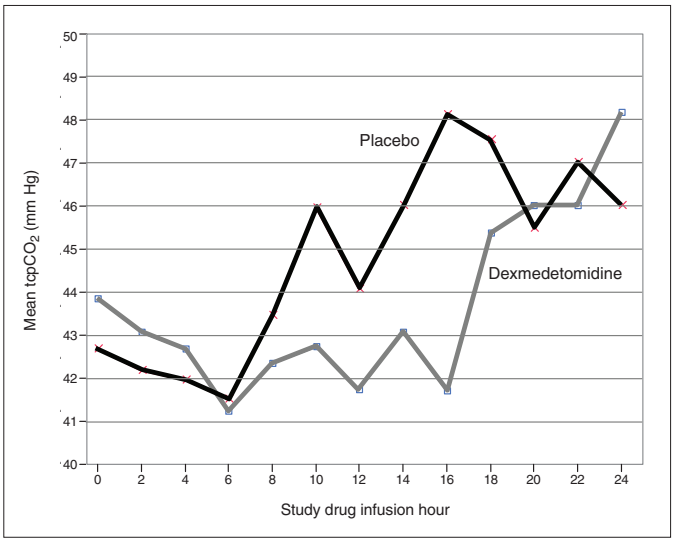

Figure 5. Transcutaneous carbon dioxide results of subjects randomized to placebo compared to intravenous dexmedetomidine.

have compromised respiratory function. Thoracotomy patients receiving opioids via a PCA pump postoperatively are at high risk for developing respiratory depression. A recent study by Overdyk et al found respiratory depression rates in postoperative patients with a PCA pump that were higher than previously reported (6).

Dexmedetomidine provides a unique type of sedation in which patients appear sleepy but are easily aroused. There is no significant respiratory depression even at high doses, and the drug possesses anxiolytic and moderate analgesic effects (24). This opioid-sparing property together with anxiolysis and sedation could provide analgesia and comfort to postthoracotomy patients and potentially reduce the number and severity of opioid-induced side effects. By modulating the release of catecholamines, dexmedetomidine decreases sympathetic tone and attenuates the stress response to surgery and anesthesia. Some data suggest that dexmedetomidine is protective of major organs and can prevent acute brain dysfunction or delirium postoperatively (25–38). This may be of great significance in this often elderly and high-risk cardiac group of patients. However, although dexmedetomidine appears to be well tolerated, there have been reports of hypotension, bradycardia, and cardiac arrest associated with its administration (39–41). As the drug modulates the release of catecholamines, vagus nerve activity is left unopposed and the patient requiring catecholamine support is in a critical situation. Therefore, signs of vagal overactivity should be treated with atropine or glycopyrrolate, and care should be given when considering the administration of dexmedetomidine to hypovolemic patients or patients in an early shock situation.

This pilot study addressed the need for adequate postoperative analgesia while at the same time decreasing the risk for respiratory depression and other untoward side effects by reducing opioid use. In this study, no patients were found to have a respiratory rate <10, although this was an intermittent measurement and brief transient changes in respiratory patterns are likely and could have been missed. The patients in this study had increased respiratory rates >50% of the time across both groups, with the percentage of the placebo group at >18 breaths per minute higher than

Table 3. Adverse events in subjects randomized to dexmedetomidine or placebo

Adverse event	Placebo†	Dexmedetomidine†	Withdrawn from study prior to randomization†	Total
Nausea	7	3	—	10
Headache	1	1	—	2
Pruritus	3	—	—	3
Constipation	2	1	—	3
Fever	2	1	—	3
Generalized weakness	1	2	—	3
Systolic blood pressure <90 mm Hg*	1	4	—	5
Systolic blood pressure <90 mm Hg†	1	2	—	3
Heart rate <50 bpm	2	0	—	2
Heart rate >110 bpm	3	1	—	4
Potassium <3.6 mEq/L	—	1	—	1
Blood glucose >110 mg/dL	—	1	—	1
Cardiac arrest/death	—	—	1	1
Multiple organ dysfunction syndrome	—	—	1	1
Stokes-Adams syndrome	—	—	1	1
Total	23	17	3	43

*Required study drug interruption.
†Subjects withdrawn from study due to concurrent beta-blocker, pneumonia, sepsis, and volume depletion.

that of the dexmedetomidine group (60% vs 51%). However, this probably represented hypoventilation with rapid shallow breathing, as CO_2 levels never declined below 40 mm Hg. Other measurements of respiratory status, such as mean pulse oximetry and mean transcutaneous carbon dioxide, were statistically similar when comparing the two groups. Yet the mean $tcpCO_2$ for both groups was above the normal 38 to 42 mm Hg, with the placebo group at a mean of 44 mm Hg and the dexmedetomidine group at a mean of 43 mm Hg. Because retaining CO_2 could have been part of an underlying medical condition in these patients, future studies should do a baseline $tcpCO_2$ reading prior to surgery in addition to immediately prior to the start of study drug, as was done in this trial.

While the mean $tcpCO_2$ by patient for all times was similar in the two groups, the readings between hours 6 and 16 were statistically significant between the two groups. The placebo group had a significantly higher $tcpCO_2$ during these times than the dexmedetomidine group with equal pain scores. At the same time, those in the dexmedetomidine group were more sedated, which may account for the raised $tcpCO_2$, as they were less likely to be hyperventilating. The explanation for the rise during this timeframe is unknown, and factors such as increased activity or decreased attention to pulmonary toilet were explored but were not consistent across all subjects.

The overall number of adverse events was higher in the placebo group, with this group more likely to develop the side effects of opioid administration and subsequently to receive additional medication to treat those side effects. Treatment of the opioid side effects of nausea and pruritus frequently led to the use of central nervous system depressants, which can put the patient at further risk for respiratory depression.

The dexmedetomidine group used 41% less opioids than the placebo group with equal analgesia. This demonstrates the known opioid-sparing properties of dexmedetomidine previously reported, thus decreasing the risk for respiratory depression (22). This study found no instances of bradycardia in the dexmedetomidine group; the only bradycardia noted was in the placebo group. Tachycardia was more prevalent in the placebo group, with the difference in heart rate significant between the two groups. This may be indicative of dexmedetomidine being cardioprotective for patients who typically have other cardiac comorbidities. No hypertension, defined as a systolic blood pressure >180 mm Hg, was noted in either group. Hypotension was found to be a risk in this study, particularly when other factors were present such as hypovolemia, sepsis, and use of concomitant medications that have the potential to decrease blood pressure, such as beta-blockers. This risk highlights the need for frequent monitoring, trained staff, and specific protocols to address hemodynamic changes.

In conclusion, the addition of dexmedetomidine to the pain management protocol for postthoracotomy patients may be safe with proper training and monitoring after patients have been stabilized on the drug for up to 24 hours. This small pilot trial showed equal analgesia and a 41% decease in opioid use in the dexmedetomidine group, thus decreasing the risk for respiratory depression in these already compromised patients. A larger trial is recommended to determine the safety of administering low-dose dexmedetomidine outside an ICU setting.

Acknowledgments

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